

REMARKS

Reconsideration of the present application based on the above amendments and the following remarks is respectfully requested.

I. Status of the Claims

Prior to the entry of the present Response, claims 11, 12, and 22-33 were pending in this application. Claims 11, 12, 22, 23, 26, 27, 31, and 33 are hereby amended, and claims 24, 25, and 30 are hereby canceled. Thus, upon entry of this amendment, claims 11, 12, and 22, 23, 26-29, and 31-33 are pending and at issue.

Claims 11, 12, 22, 23, 26, 27, 31, and 33 have been amended to better comply with U.S. claim drafting practice. Claim 1 has additionally been amended to call for “an ether solvent in which atorvastatin calcium is not soluble or is poorly soluble.” Support for this amendment is found in claim 25 as originally filed, and in the specification at pages 9-10, bridging paragraph.

No new matter is added by way of this Amendment and Response.

II. Examiner Interview

Applicants would like to thank Examiner Sun Jae Loewe for the courtesy extended to applicant's agent Andrew Larsen during the telephonic interview of April 29, 2010, where the parties discussed the nature of the current enablement rejection and potential strategies for traversing that rejection. No agreement was reached during the interview.

III. Rejection under 35 U.S.C. § 112, first paragraph (enablement)

Claims 11, 12, 22, 23 and 27 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner asserts that the specification, while being enabling for making

amorphous atorvastatin calcium via the processes of Examples 1-5, does not reasonably provide enablement for making amorphous atorvastatin calcium via the full scope of the claimed processes. To support her rejection, the Examiner contends that the “[t]he state of the art for preparing polymorphic forms of any given compound is unpredictable” because (1) “[t]he number or existence of solid forms cannot be predicted,” (2) “[t]he more diligently any system is studied the larger the number of polymorphs *discovered*,” and (3) “[i]t is not commonly known in the art, or predictable, how different polymorphs are made.” (See November 5th, 2008 Office Action at page 6, citing Chawla et al.). Accordingly, the Examiner considers the level of unpredictability in the field of polymorphs to be high, such that undue experimentation would be required to practice the full scope of the claimed processes. In the Examiner’s view, the enablement requirement could be met if applicants narrowed the solvents claimed for precipitation of amorphous atorvastatin calcium to that used in the working examples (i.e., diisopropyl ether). The rejection is respectfully traversed based on the above amendments and the foregoing remarks.

Claim 1 has been amended to call for precipitating amorphous atorvastatin calcium from an organic phase comprising the addition “an ether solvent in which atorvastatin calcium is not soluble or is poorly soluble” to the organic phase. Such an amendment is fully supported and enabled by the specification at page 9-10, wherein it is taught that “Subsequently, a 0.4 fold to a 0.8 fold volume of a solvent ... in which atorvastatin calcium is not soluble or is low soluble, is optionally added. As solvent, ether, preferably diisopropyl ether, may be used.” Although the Examiner contends that the specification is only enabling for precipitating amorphous atorvastatin calcium using diisopropyl ether specifically, the specification clearly teaches that diisopropyl ether is just one example within the class of ether solvents that the skilled artisan could use to precipitate amorphous atorvastatin calcium. The class of ether solvents suitable to practice the present invention includes *any* ether solvent wherein atorvastatin calcium is insoluble or is poorly soluble. Accordingly, even though the working examples employ only diisopropyl ether, the specification provides sufficient direction and guidance for the skilled artisan to use other ether solvents for precipitation of amorphous atorvastatin calcium.

The amount of direction and guidance needed to enable the invention is inversely proportional to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d. 833, 839 (CCPA 1970). The Examiner has found the present claim non-enabled because, in her view, the field of polymorphic crystal forms is highly unpredictable (*supra*). Applicants respectfully submit, however, that predictability in the art of amorphous crystal forms should be viewed apart from predictability in the art of crystalline polymorphs. *Grant & Hackh's Chemical Dictionary* (New York, McGraw Hill, 5th Ed. 1987; Exhibit A) defines "amorphous" as "(1) unorganized[, or] (2) describing a solid substance which does not crystallize and is without definite geometrical shape." In addition, *Hawley's Condensed Chemical Dictionary* (New York, Von Nostrand Reinhold, 13th Ed. 1997; Exhibit B) defines amorphous as "[n]on-crystalline, having no molecular lattice structure, which is characteristic of the solid state." Amorphous forms are well known in the pharmaceutical art as shown in, for example, Yu et al. (*Advanced Drug Delivery Reviews*, 48 (2001), 27-42; Exhibit C) which distinguishes amorphous solids as follows: "[a]n amorphous solid ([a] glass) can be defined with reference to a crystalline solid: similar to a crystalline solid, an amorphous solid may have short range molecular order ... ; but unlike a crystalline solid, an amorphous solid has no long-range order of molecular packing[.]" (Exhibit C, pg. 28, 1st full paragraph. Based on the definitions above, an amorphous form can be distinguished from all other crystal forms because it is an unorganized, disordered, and non-crystalline. Accordingly, although the "number or existence of solid forms cannot be predicted" (*supra*), applicants respectfully submit that all solids have an amorphous state, which is *any* solid state having "no long-range order of molecular packing" (i.e., it is simply a solid form that has not been allowed to crystallize into a highly ordered crystalline array). In fact, "[a]morphous solids [are known] to *exist widely* and impart special properties to pharmaceutical products." (Exhibit C, pg. 39, 2nd full paragraph; emphasis added). Thus, unlike a distinct crystalline form having a defined structure, the existence of an amorphous form of a solid is *highly predictable*.

Moreover, applicants respectively submit that the method of precipitation to generate a composition comprising an amorphous form is well known in the art, including precipitation with a

“solvent in which [a pharmaceutical compound] is not soluble or is poorly soluble.” For example, even “poor glass formers ([i.e., compounds that are highly crystalline,] e.g., mannitol) can be made amorphous *by deliberately preventing crystallization. Familiar routes to the amorphous state include quenching of melts, rapid precipitation by antisolvent addition, freeze drying ... , spray drying ... , and introduction of impurities*” (Exhibit C; emphasis added). Not only was precipitation using an antisolvent (i.e., a solvent in which a compound is insoluble or poorly soluble) well known in the art, but precipitation was regarded as one of “[t]he four most common means by which amorphous character is induced in a solid.” Hancock et al. *J. Pharmaceutical Sci.* 86 (1997), 1-12 at page 1, 1st full paragraph (Exhibit D) (The four most common means by which amorphous character is induced in a solid ... are condensation from the vapor state, supercooling of the melt, mechanical activation of a crystalline mass, and *rapid precipitation from solution*). Thus, the skilled artisan would know how to make a composition comprising an amorphous solid using techniques that were well known in the art, including precipitation with an antisolvent, which is a method used in the currently pending claims.

Accordingly, applicants respectfully submit that one of ordinary skill in the art could make and use the *full scope* of the presently claimed invention based on the specification and without undue experimentation. The quantity of experimentation necessary to identify other ether solvents in which atorvastatin is insoluble or is poorly soluble would not be undue experimentation, because precipitation with an antisolvent is a well known technique for preparing amorphous forms. Thus, all that would be required to practice this step of the claimed invention is to test an ether solvent’s ability to solubilize atorvastatin calcium. This amount of experimentation would be routine, and therefore would not preclude patentability of the currently pending claims for lack of enablement.

In sum, although the number or existence of solid forms cannot be predicted, amorphous forms of solids are highly predictable, and include any form of that solid wherein there is no long-range order in the solid (i.e., it is not crystalline). Even if a larger number of crystalline polymorphs were discovered for a known compound, this would not affect the predictable nature of an

amorphous solid, which is presumed to exist for most substances. Based on the above discussion, precipitation as a step in making amorphous forms of pharmaceutical agents is *commonly known in the art, and therefore predictable*. Rapid precipitation using an antisolvent, in particular, a technique employed as a step in the currently pending claims is also known and appreciated in the art. Therefore, in view of the all foregoing reasons, one of ordinary skill in the art would be able to generate a composition comprising an amorphous solid using the precipitation step recited in claims 11, 12, 22, 23 and 27 without undue experimentation. Accordingly, claims 11, 12, 22, 23 and 27 are fully enabled, and applicants respectfully request that this rejection be withdrawn.

Nor is this submission inconsistent with the non-obviousness of the claimed subject matter as a whole. The present claims recite much more than crashing amorphous atorvastatin calcium out of solution with an ether antisolvent. They recite a series of steps prior to precipitation which result in an improved preparation of an amorphous atorvastatin calcium product from one pot, without the need to isolate an intermediate solid product and without the need to separate solid impurities. In fact, applicants have “ascertained that the key factor in this process is the selection of the organic solvent used in the step of forming calcium salt of atorvastatin” which, combined with the other claimed steps, provides for a superior process over the prior art (*See* specification at page 4). These advantages arise from the practice of the presently claimed methods *as a whole* and, therefore, the fact that rapid precipitation was well known in the art is of little relevance to an obviousness inquiry.

CONCLUSION

Applicants respectfully submit that this application is now in condition for allowance. Reconsideration and prompt allowance of which are respectfully requested.

The Examiner is invited to contact the undersigned if any additional information or assistance is required.

Applicants believe that no additional fee is due in connection with the filing of this response. If any additional fee is due, or overpayment made, with regard to this response, Applicants authorize the Director to charge any such fee, and credit any overpayment, to Deposit Account No. 13- 2725.

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